METHYLPHENIDATE, LISDEXAMFETAMINE, DEXAMFETAMINE, GUANFACINE, and ATOMOXETINE FOR ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD) IN CHILDREN AND ADOLESCENTS
Shared Care Protocol

- **For children ≥6 years old, and adolescents <18 years old.**
- **This protocol covers the use of methylphenidate by Oxford University Hospitals and methylphenidate, lis-dexamfetamine, dexamfetamine, guanfacine and atomoxetine by Oxford Health.**

This protocol provides prescribing and monitoring guidance for ADHD treatment. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc, and the BNF and the Oxfordshire Shared Care Protocol Best Practice Guidelines.

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1. SUMMARY

1. ADHD is a heterogeneous behavioural syndrome characterised by the core symptoms of hyperactivity, impulsivity and inattention. While these symptoms tend to cluster together, some people are predominantly hyperactive and impulsive, while others are inattentive.
2. Methylphenidate, lisdexamfetamine, dexamfetamine, atomoxetine, and guanfacine, are indicated as part of a comprehensive treatment programme for ADHD in children and young people when non-pharmacological measures alone prove insufficient.
3. NICE ADHD guideline[1] states that treatment should only be initiated by an appropriately qualified healthcare professional with expertise in ADHD. Young people with ADHD should normally be transferred to adult psychiatric services if they continue to have significant symptoms of ADHD or other co-existing conditions, with adult services carrying out a comprehensive assessment of the person with ADHD.
4. ADHD continues into adulthood in up to two thirds of patients. Studies have shown that stimulants work on core symptoms in adults with ADHD. Although not all methylphenidate products are licensed for use in adults, NICE recommends methylphenidate as one of the first line treatments of adults diagnosed with ADHD, with lis-dexamfetamine as an alternative first line in this age group. For further guidance about the management of ADHD in adults refer to the adult treatment pathway.
5. NICE recommends that continued prescribing and monitoring of drug therapy may be performed by general practitioners, under shared care arrangements, ensuring clear lines of communication between primary and

secondary care are maintained.

6. When a consultant psychiatrist for children/adolescents feels that the patient may benefit from continued care by the primary care team then he/she may seek the agreement of the GP concerned to share care, providing the following conditions are met:
    a. The patient's condition is stable.
    b. The dose of ADHD treatment is stable (this includes ensuring that a patient is stable following a switch from an immediate to a prolonged release preparation).
    c. The GP is provided with sufficient information to ensure they are confident to adequately monitor the patient.
    d. Support and advice regarding all aspects of therapy will be provided by the specialist team.

    If a GP is not confident to undertake these roles then he or she is under no obligation to do so.
7. If patients from abroad come to stay temporarily or permanently in Oxfordshire and the medication or formulation of the medication they are prescribed is not covered by these guidelines, they will need to obtain their medication from their country of origin or have their treatment reviewed. Any patients unable to obtain a supply from their country of origin or who request repeat medication for ADHD, will need referring into the appropriate clinic for confirmation of diagnosis according to ICD-10 diagnostic criteria. Where medication is indicated, the closest alternative within these guidelines will be prescribed. As there are different thresholds for diagnosis of ADHD in other countries, any patients prescribed medication within this guidance must fit into ICD-10 diagnostic criteria for ADHD to receive treatment.
8. Patients who have been diagnosed and treated privately may then request that further treatment be provided within the NHS. See Thames Valley Priorities Committee Commissioning Policy Statement 35. In this case, the patient may be transferred to the NHS and should be re-assessed for NHS treatment within the same regime of priorities applicable to NHS patients. Patients will need referring into the appropriate clinic for confirmation of diagnosis according to ICD-10 diagnostic criteria. Where medication is indicated, the most appropriate treatment for that individual will be initiated or existing medication continued, if appropriate, according to these guidelines.

2. BACKGROUND

For a diagnosis of ADHD, based on a complete history and evaluation of the patient, symptoms of hyperactivity/impulsivity and/or inattention should:

- Meet the diagnostic criteria in DSM-IV or ICD-10 (hyperkinetic disorder)[1], **and**
- Be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings, **and**
- Be pervasive, occurring in two or more important settings including social, familial, educational and/or occupational settings.

Current treatments for ADHD include a range of social, psychological, and behavioural interventions, which may be focused on the child/patient, parents and/or caregivers, or teachers.

When deciding to treat children or young people aged 5 years and over with medication, NICE recommends the following *(N.B. this shared care protocol applies to children aged 6 years and older):*

- Methylphenidate (either short or long acting) as the first line pharmacological treatment for children aged 5 years and over and young people with ADHD.
- Switching to lisdexamfetamine if there has not been enough benefit, in terms of reduced ADHD symptoms and associated impairment, following a 6-week trial of methylphenidate at an adequate dose.
- Consider dexamfetamine if ADHD symptoms are responding to lisdexamfetamine, but where the longer effect profile is not tolerated.
- Offer atomoxetine or guanfacine if:
    - they cannot tolerate methylphenidate or lisdexamfetamine or
    - their symptoms have not responded to separate 6-week trials of lisdexamfetamine and methylphenidate, having considered alternative preparations and adequate doses.
- Offer the same medication choices to people with ADHD and anxiety disorder, tic disorder or autism spectrum disorder as other people with ADHD.

General treatment principles

- In order to optimise drug treatment, the initial dose should be titrated against symptoms and adverse effects in line with dosing guidance in the BNFc. Progress should be reviewed regularly and clearly documented.
- Dose titration should be slower and monitoring more frequent in the presence of neurodevelopmental disorders, mental health conditions, or physical health conditions.
- If adverse effects are troublesome a reduction in dose should be considered.
- Treatment response for all drugs should be reviewed at least annually by the specialist. This should include a comprehensive assessment of clinical need, benefits and adverse effects - taking into account views of patient and carers; the effect of missed doses, and planned dose reductions or brief periods of no treatment.
- After titration and dose stabilisation, NICE states that prescribing and monitoring of ADHD medication should be carried out under Shared Care Protocol arrangements with primary care.

3. RESPONSIBILITIES AND ROLES[3]

Specialist responsibilities
1. Oxfordshire Consultant Paediatrician or Oxford Health CAMHS Psychiatrist: confirm the diagnosis of ADHD in children/adolescents following a full assessment. Assessment should include personal, educational, occupational and social functioning, and assessment of any co-existing conditions e.g. drug misuse, personality disorders, emotional problems and learning difficulties
2. **This SCP applies to ≥6 to <18-year olds**.
* For the following patients, please refer to the adult ADHD pathway protocol:
-- Those with a diagnosis of ADHD transferring from CAMHS at age 18
-- 18-year olds with a diagnosis of ADHD, discharged by community paediatrics who have been referred to adult psychiatry
-- New patients (≥18) without an ADHD diagnosis.
* For patients <6 years of age, treatment should remain under the specialist in secondary care.
3. Decide on appropriate drug treatment, discuss benefits and adverse effects with the patient and/or parents/carer and provide written information where appropriate. In the case of atomoxetine, this should also include an explanation of the very rare risk of adverse hepatic reactions, what symptoms to look out for and what action to take should they occur.
4. Complete and record the following baseline assessments:
a. A medical history, taking into account conditions that may be contraindications for specific medicines
b. Any concomitant medications,
c. Height and weight
d. Pulse and blood pressure
e. A cardiovascular assessment. An electrocardiogram (ECG) is not needed before starting stimulants, atomoxetine or guanfacine, unless the person has any of the features listed below, or a co-existing condition that is being treated with a medicine that may pose an increased cardiac risk.
Refer for a cardiology opinion before starting medication for ADHD if any of the following apply:
• history of congenital heart disease or previous cardiac surgery
• history of sudden death in a first-degree relative under 40 years suggesting a cardiac disease
• shortness of breath on exertion compared with peers
• fainting on exertion or in response to fright or noise
• palpitations that are rapid, regular and start and stop suddenly (fleeting occasional bumps are usually ectopic and do not need investigation)
• chest pain suggesting cardiac origin
• signs of heart failure
• a murmur heard on cardiac examination
Refer to a paediatric hypertension specialist before starting medication for ADHD if blood pressure is consistently above the 95th centile for age and height.
5. Titrate the dose against symptoms and adverse effects in line with the BNFc until dose optimisation is

achieved [i.e. reduced symptoms, positive behaviour change, improvements in education, employment and relationships, with tolerable adverse effects]..The patient's progress should be reviewed regularly during the titration phase (for example by weekly telephone contact). Record symptoms and adverse effects at each dose change

6. Prescribe for a patient who is being switched from one product to another e.g. an immediate to a prolonged release methylphenidate preparation – usually for a period of 1 month – until they are re-stabilised.
7. Consider specific school policies on the use of medicines in schools, if multiple daily doses in school age children are required.
8. Follow the ongoing physical monitoring schedule below. Refer patients to a cardiologist if symptoms suggestive of cardiac disease develop.
9. Continue prescribing in children under 6 years old.
10. Patients aged 6 years or older who's medication is stabilised may qualify for shared care. At this stage the GP may be contacted to request shared care.
11. NICE recommends that ADHD medication is reviewed at least annually by the specialist. The review should include a comprehensive assessment of the preference of the child/young person, benefits, adverse effects, clinical need and whether medication has been optimised, impact on education/employment, effect of missed doses, planned dose reductions, and periods of no treatment, effect of medication on existing or new mental health, physical health or neurodevelopmental conditions. The need for support and type of support if medication has been optimised but ADHD symptoms continue to cause significant impairment should also be considered. Maintaining close clinical contact by means of a telephone review may be beneficial for some patients.
12. Carry out the physical monitoring according to the schedule in section 4 below.
13. Consider trial periods of stopping medication or reducing the dose when assessment of the overall balance of benefits and harms suggests this may be appropriate. If the decision is made to continue medication, the reasons for this should be documented.
14. Communicate diagnosis, behavioural problems, cognitive and functional scores, any changes of medication (including dose) and results of physical monitoring to the GP.
15. Support and advise the prescribing GP as needed.
16. Communicate to the GP non-attendance of patients at outpatient appointments. The patient should be sent a letter asking them to make another appointment as soon as possible. The specialist must evaluate the need to discontinue treatment in patients who DNA more than 2 or 3 consecutive appointments.
17. Report serious adverse events to the MHRA and inform the GP.
18. Monitor patients for the risk of diversion, misuse and abuse of stimulant medication.
19. To refer young people who reach 18 to adult services only if they appear to meet the criteria for clusters 4-17 and who may need to be transitioned to adult psychiatric services (see adult ADHD pathway protocol).
20. To review the ongoing need for ADHD treatment in young people reaching 18 who do not meet criteria for clusters 4-17, discharging them back to the care of the GP with advice regarding ongoing treatment if deemed to be necessary (see adult ADHD pathway protocol).

General Practitioner responsibilities
1. Respond promptly to any request to share care by following the guidance in the Shared Care Protocol Best Practice Guidelines document. 2. Ensure a full understanding of the responsibilities for managing a patient taking medication for ADHD including identification of adverse-effects in line with the relevant SPC. 3. Provide repeat prescriptions after stabilisation. 4. Be aware that methylphenidate, lisdexamfetamine and dexamfetamine are liable to misuse, abuse or diversion. Discuss any concerns with the specialist. 5. Report any change in symptom control that they become aware of to the specialist. 6. Assess the patient for adverse effects and liaise with the specialist if necessary. 7. Report to and seek advice from the specialist on any aspect of patient care which is of concern to the GP and which may affect treatment. Refer anyone who develops signs of cardiovascular disease to a cardiologist and contact the specialist for advice about dose reduction or cessation of treatment. 8. Report adverse events to the specialist and the MHRA. 9. Follow written advice from the specialist on any changes in treatment. 10. Notify the specialist of the patient's failure to attend appointments. 11. Be aware that school policies on the use of medicines differ and consult with the specialist if a child/ adolescent changes to a school with a policy that affects the use of multiple daily doses of medicines.

Patient's/Carer's role
1. Attend all appointments with the GP and Specialist. 2. Report any adverse effects to the Specialist or GP whilst under treatment. 3. Share any concerns they have in relation to treatment. 4. Ask the Specialist or GP if they do not have a clear understanding of their treatment. 5. Allow at least 5 days' notice when requesting further prescriptions

4. ONGOING PHYSICAL MONITORING SCHEDULE RECOMMENDED BY NICE (*carried out by Specialist)*

	Frequency	Comments	Intervention
Height	6-monthly	Plot on a centile chart	If growth is affected significantly, consider a planned break in drug treatment over the school holidays to allow "catch-up" growth.
Weight	6-monthly	Plot on a centile chart	Strategies to reduce weight loss, or manage decreased weight gain include: • Taking medication with or after food rather than before meals • Eating additional meals or snacks early morning or late evening when stimulant effects have worn off • Obtaining dietary advice and eating high calorie foods of good nutritional value If weight loss persists consider a possible dose reduction, a planned break from treatment or changing medication. An increase in weight/BMI may occur in patients taking guanfacine.
Pulse	Before and after each dose change	Record on a chart	If there is sustained resting tachycardia (more than 120beats per minute) or arrhythmia, reduce the dose and refer to a Paediatrician.

	and 6-monthly thereafter.		If there is significant bradycardia in a person taking guanfacine dose reduction or withdrawal of treatment may be necessary.
Blood pressure		Plot on a centile chart	If sBP is greater than the 95th percentile or there is a clinically significant increase (e.g. 15 – 20 mmHg) measured on two occasions, reduce the dose and refer to a Paediatrician. If a person taking guanfacine has sustained orthostatic hypotension or fainting episodes, reduce the dose. Switching to an alternative treatment may be necessary.

5. PRESCRIBING INFORMATION

Formulary status

All medicines approved for prescribing for treatment of ADHD within Oxfordshire are listed as amber protocol on the formulary. They are restricted to being initiated by secondary care specialists with ongoing prescribing by GPs in line with this Shared Care Protocol.

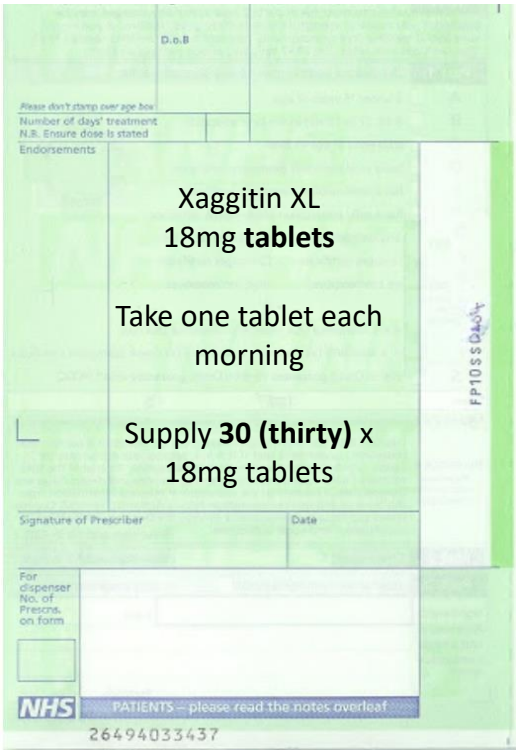
Legal status

Drug	Schedule	Max supply duration	Validity of prescription from date signed
Methylphenidate	2 (CD)	30 days	28 days
Lisdexamfetamine	2 (CD)	30 days	28 days
Dexamfetamine	2 (CD)	30 days	28 days
Atomoxetine	POM	6 months	6 months
Guanfacine	POM	6 months	6 months

Prescribing Controlled Drugs

Methylphenidate, lisdexamfetamine and dexamfetamine are controlled drugs, subject to safe custody and specific regulations for prescribing. The prescription must include:

- The **formulation** and **strength** of the drug
- The **dose**
- The **total quantity** written in words **and** figures (see BNF for more details)

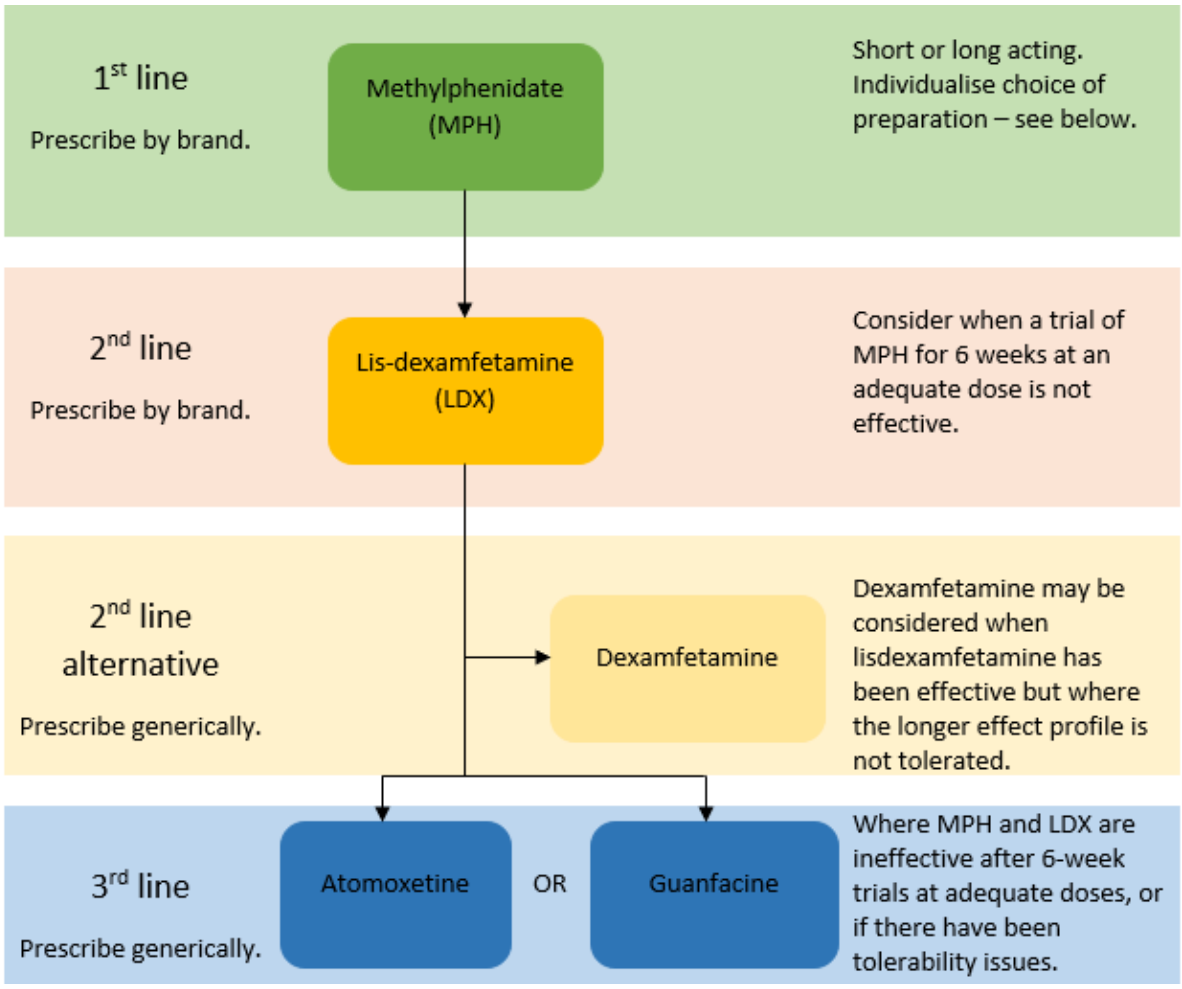


An electronic prescription is acceptable, but the prescriber's signature must be handwritten and indelible. Advanced electronic signatures are acceptable for Schedule 2 and 3 controlled drugs where the Electronic Prescribing Service (EPS) is in place.

A pharmacist can legally amend a controlled drug prescription if they are satisfied that they know what the prescriber intended, only in the following circumstances:

1. Minor typographical errors or spelling mistakes.
2. To add in either the words or the figures to the total quantity if the prescriber has missed one or the other off.

Treatment algorithm for children 5 years or over and adolescents



Methylphenidate

A brief summary of information is included below, but for full prescribing information please refer to the manufacturer's SPCs at: www.medicines.org.uk/emc/

Licensed indications.

Licensed as part of a comprehensive treatment programme for ADHD in children aged 6 years and over and adolescents when non-pharmacological measures alone prove insufficient.

Formulations included in shared care.

Immediate release

- tablets: 5 mg, 10 mg, 20 mg
- Liquid: Methylphenidate 5mg/5ml oral suspension 150ml (Dug Tariff Special, unlicensed) – restricted for use in patients who require an immediate release formulation but can't swallow tablets.

Prolonged release formulations

Extended or modified release preparations are more expensive than immediate release preparations but may be useful in certain situations e.g. to avoid the need to take medicines at school.
The preparations differ in their formulation (tablet, capsule), available strengths, pharmacokinetics (release profiles, duration of action), and how they should be administered (swallow whole, open capsule and sprinkle onto food etc.). These differing profiles allow the clinician to individualise treatment. Choice should therefore be tailored to each individual patient.

Up to 8-hour duration of action:

- 50:50 release profile
  Medikinet XL® capsules (5, 10, 20, 30, 40, 50, & 60mg)

- 30:70 release profile
  Equasym XL® capsules (10, 20, & 30 mg)

12-hour duration of action:

- 25:75 release profile
  Xaggitin XL® or Delmosart® modified release tablets (18, 27, 36, & 54mg)

  Xaggitin XL and Delmosart are Oxford Health's **formulary choice** *when a 12-hour duration of action is required.*
  Both are bioequivalent∞ to Concerta XL®.
  Xaggitin XL is the most cost-effective preparation.

- 22:78 release profile
  Concerta XL® tablets (18, 27, 36, 54mg)

  Concerta XL is **restricted** within Oxford Health and should only be prescribed in exceptional cases where Xaggitin XL or Delmosart have been deemed to be not suitable. This includes patients who have switched from a stable dose of Concerta XL and experienced a clear change in symptom control – see note about bioequivalence (∞) below.
  It may also be prescribed temporarily where there are supply issues with *both* Xaggitin XL and Delmosart (see page 9).

∞ *Bioequivalence*

Demonstrating bioequivalence is an essential requirement of licence applications for generic medicinal products. Single doses of the reference drug and the test-generic drug are given to healthy volunteers. Measurements over time are taken to calculate the maximum concentration (Cmax) and the area under the curve (AUC). Ratios of test - reference mean values for these key parameters must be within 90% confidence limits of 80% to 125% to demonstrate bioequivalence.
Most patients will be able to switch between the original brand and branded generics without concern. However, it is possible that a minority of patients could experience a change in symptom control following a switch. If this has been clearly demonstrated, the patient can be switched back to and maintained on Concerta XL. This should be clearly documented so that there are no future attempts made to switch.

Contraindications and precautions.	Refer to the manufacturer's SPCs at www.medicines.org.uk/emc/
Dose, titration and administration.	Careful dose titration is necessary at the start of treatment. Recommended starting dose using IR is 5 mg once or twice daily (e.g. at breakfast and lunch), increasing if necessary, by increments of 5 - 10 mg daily at no more than weekly intervals, according to tolerability and efficacy. If twice or three times daily dosing is impracticable, an XL preparation may be used. Doses up to a total maximum of 90 mg/day* in children and young adults (6 – 17 years) may be indicated. For information on dose equivalents between different formulations, see table 1. For administration information, see table 2. **108mg/day if using Xaggitin XL, Delmosart, or Concerta XL [A total daily dose of 15 mg of standard-release formulation methylphenidate is considered equivalent to 18 mg once daily of these formulations. This is due to the way these tablets are made, as some methylphenidate remains inside the tablet core].*
Onset of action.	An initial of effect is usually within 30 minutes – 1 hour but is dependent on the formulation. It may take a few weeks for the full effect to be seen
Duration of effect.	Formulation dependent – see table 2.
Missed doses.	Immediate release preparations can be taken as they are remembered unless this is after mid to late afternoon or within two hours of the next dose being due. In this case, do not take the missed dose, but continue with your next due dose at the usual time. Re-titration is not necessary. Modified release products can be taken as soon as you remember unless this is after mid to late morning. In this case, do not take the dose, but continue with your usual dose the following day. Re-titration is not necessary. Extended release preparations taken in the afternoon or evening are likely to make it more difficult to sleep.
Discontinuation.	Methylphenidate should be stopped if there has been no improvement in symptoms after about six weeks at an appropriate dose. Methylphenidate can often be stopped abruptly if the dose is low. Suddenly stopping higher doses may cause withdrawal effects and so a gradual reduction in dose may be more appropriate. Withdrawal symptoms can include extreme tiredness, increased activity, being irritable, poor sleep, increased appetite and depression. It is usually safe to recommend treatment breaks particularly from relatively low doses without the need for downward titration or re-initiation e.g. during school holidays or at weekends.

Adverse effects – some of the more common effects. (see SPC for full list).

Frequency	Effect	Additional information and management
Very common (≥ 1/10)	Headache	Usually transient. Paracetamol may help.
	Insomnia	Dose timing or formulation change may be necessary.
	Nervousness	Usually transient.
Common (≥ 1/100 to < 1/10)	Nausea, vomiting, GI upset	Mainly at the start of treatment and usually transient. Might be helped by taking dose with food.
	Reduced appetite and weight loss	See monitoring schedule for guidance.
	Cough and nasopharyngitis	Usually transient.
	Tachycardia	See monitoring schedule for guidance.
	Dizziness	Usually transient.

	Uncommon (≥ 1/1,000 to < 1/100)	Changes in mood	Development of new or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.
		Tics	If tics occur, consider whether they are medication related and whether tic related impairment outweighs the benefits of ADHD treatment. Tic severity naturally waxes and wanes.
Interactions	See stimulant interaction table 3.		
Patient information leaflets	https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/91/ALL/		

Table 1. Equivalent dose (in mg) by formulation, including unlicensed doses[3]

Formulation	IR	Xaggitin XL®	Delmosart®	Concerta XL	Equasym XL	Medikinet XL
Equivalent doses	5	-	-	-	-	5
	10	-	-	-	10	10
	15	18	18	18	-	15 (10 + 5)
	20	-	-	-	20	20
	-	27	27	27	-	-
	30	36	36	36	30	30
	40	-	-	-	40 (2 x 20)	40
	45	54	54	54	-	45 (40 + 5)
	50		-	-	50 (20 + 30)	50
	60	72* (2 x 36)	72* (2 x 36)	72* (2 x 36)	60 (2 x 30)	60
	90	108* (2x54)	108* (2 x 54)	108* (2 x 54)	90* (3 x 30)	90* (60 +30)
* unlicensed doses						

Table 2. Differences in extended release methylphenidate formulations (*adapted from J Clin Pharm 2009)*

	Xaggitin XL, Delmosart, Concerta XL tablets	Medikinet XL capsules	Equasym XL capsules
Composition (immediate/ extended release)	25% / 75% (Xaggitin XL and Delmosart) 22% / 78% (Concerta XL)	50% / 50%	30% / 70%
Release profile	Maximum plasma concentration at 1-2 hours, second peak at 6-8 hours.	Maximum plasma concentration reached rapidly, second peak at 3-4 hours.	Maximum plasma concentration at 1.5 hours, followed by a second peak at 6 hours.
Duration of action	Up to 12 hours	At least 7 hours	Up to 8 hours
Administration	Swallow whole with liquid. Must not be chewed, crushed or divided	Can be swallowed whole with liquid or opened and the contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately. Capsules and	Can be swallowed whole with liquid or opened and the contents sprinkled onto a small amount (tablespoon) of applesauce or yoghurt and given immediately. Capsules

Managing methylphenidate 12- hour extended release product shortages

Xaggitin XL,Delmosart and Concerta XL can be prescribed interchangeably if there is a shortage of one or more of these products, without the need to contact secondary care prescribers. All three products are bioequivalent to one another. Concerta XL is less cost effective than Delmosart or Xaggitin XL. Xaggitin XL is the most cost-effective option. If Xaggitin XL is not available, Delmosart can be prescribed and vice versa. Concerta XL should only be prescribed as an alternative when both Xaggitin XL and Delmosart are unavailable.

Lisdexamfetamine

		contents not to be crushed or chewed	and contents not to be crushed or chewed
Food requirements	Can be taken with or without food	To be taken with or after breakfast	To be taken before breakfast
Frequency	Once daily in the morning	Once daily in the morning	Once daily in the morning
IR equivalent dosing	Three times daily	Twice daily	Twice daily

A brief summary of information is included below, but for full prescribing information please refer to the manufacturer's SPCs at: www.medicines.org.uk/emc/

Licensed indications	Elvanse is licensed as part of a comprehensive treatment programme for ADHD in children aged 6 to 17 years when response to previous methylphenidate treatment is considered clinically inadequate.
Formulations included in shared care	Elvanse extended release capsules (20, 30, 40, 50, 60, & 70 mg)
Contraindications and precautions	Refer to the manufacturer's SPC at www.medicines.org.uk/emc/
Dose, titration and administration	Careful dose titration is necessary at the start of treatment, based on response and tolerability. **6 – 17 years:** Start at 20mg or 30 mg once in the morning. Increase by 10mg or 20mg increments at approximately weekly intervals if indicated. The maximum recommended dose is 70 mg daily; higher doses have not been studied. To be swallowed whole or the contents can be emptied into a liquid or soft food (yoghurt, orange juice) before swallowing.
Onset of action	Onset of action is usually within 1 – 2 hours of a dose. It may take a few weeks for the full effects to be seen.
Duration of effect	Duration of effect is approximately 13 hours.
Missed doses	Take the dose as soon as you remember unless this is after mid to late morning. In this case, do not take the dose, but continue with your usual dose the next day. Re-titration is not necessary. Extended release preparations taken in the afternoon or evening are likely to impact on sleep onset.
Discontinuation	LIsdexamfetamine should be stopped if there has been no improvement in symptoms after about six weeks at an appropriate dose.

Lisdexamfetamine can often be stopped abruptly if the dose is low. Suddenly stopping higher doses may cause withdrawal effects and so a gradual reduction in dose may be more appropriate. Withdrawal symptoms can include extreme tiredness, increased activity, being irritable, poor sleep, increased appetite and depression.

Adverse effects – some of the more common effects. See SPC for full list

Frequency	Effect	Additional information and management
Very common (≥ 1/10)	Headache	Usually transient. Paracetamol may help.
	Insomnia	Dose timing or formulation change may be necessary.
	Reduced appetite and weight loss	See monitoring schedule for guidance.
Common (≥ 1/100 to < 1/10)	Nausea, vomiting, GI upset	Mainly at the start of treatment and usually transient. Might be helped by taking dose with food.
	Nervousness	Usually transient.
	Tachycardia	See monitoring schedule for guidance.
	Dizziness	Usually transient.
Uncommon (≥ 1/1,000 to < 1/100)	Changes in mood	Development of new or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.
Frequency not specified	Tics	If tics occur, consider whether they are medication related and whether tic related impairment outweighs the benefits of ADHD treatment. Tic severity naturally waxes and wanes.

Interactions

See stimulant interactions - table 3.

Patient information leaflets

https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/75/ALL/

Dexamfetamine

A brief summary of information is included below, but for full prescribing information please refer to the manufacturer's SPCs at: www.medicines.org.uk/emc/

Licensed indications	Licensed as part of a comprehensive treatment programme for refractory ADHD in children ages 3 years and older. Dexamfetamine is not licensed for the treatment of ADHD in adults. Use is reserved for patients who respond well to lisdexamfetamine, but where a shorter acting option is required.
Formulations included in shared care	*Immediate release:* • Tablets: 5mg, 10mg, 20 mg • Liquid: Dexamfetamine 5mg/5ml oral solution sugar free 150 ml (Essential Pharmaceuticals Ltd) – restricted for use in patients who can't swallow tablets
Contraindications and precautions	Refer to the manufacturer's SPC at www.medicines.org.uk/emc/ (tablets) and to https://products.mhra.gov.uk/ (liquid)
Dose, titration and administration	Careful dose titration is necessary at the start of treatment, based on response and tolerability. Tablets can be divided to facilitate swallowing if needed. Take at the same times each day, preferably with or after food.

Age	Usual starting dose	Maximum dose
3 – 5 years	2.5 mg daily increased if necessary by 2.5 mg at weekly intervals.[13]	Usual upper limit is 1 mg/kg daily up to 20 mg daily (some children require 40 mg or more for optimal response).
>6 years	5 mg once or twice a day (breakfast and lunch) increased if necessary at weekly intervals by 5 mg. Maintenance dose is given in two to four divided doses.	

Onset of action	Onset of action is usually within 20 – 30 minutes of a dose. It may take a few weeks for the full effects to be seen.
Duration of effect	Duration of action 3 - 4 hours.
Missed doses	Take the dose as soon as you remember unless this is after mid to late afternoon or within two hours of the next dose being due. In this case do not take the dose, but continue with your next due dose at the usual time. Re-titration is not necessary.
Discontinuation	Dexamfetamine can often be stopped abruptly if the dose is low. Suddenly stopping higher doses may cause withdrawal effects and so a gradual reduction in dose may be more appropriate. Withdrawal symptoms can include extreme tiredness, increased activity, being irritable, poor sleep, increased appetite and depression.

Adverse effects – some of the more common effects.

Frequency	Effect	Additional information and management
Very common (≥ 1/10)	Headache	Usually transient. Paracetamol may help.
	Insomnia	Dose timing or formulation change may be necessary.

See SPC for full list		Reduced appetite and weight loss	See monitoring schedule for guidance.
		Nervousness	Usually transient.
	Common (≥ 1/100 to < 1/10)	Nausea, vomiting, GI upset	Mainly at the start of treatment and usually transient. Might be helped by taking dose with food.
		Tachycardia	See monitoring schedule for guidance.
		Dizziness	Usually transient.
		Changes in mood	Development of new or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.
	Very rare (<1/10,000)	Tics	If tics occur, consider whether they are medication related and whether tic related impairment outweighs the benefits of ADHD treatment. Tic severity naturally waxes and wanes.
Interactions	See stimulant interactions - table 3.		
Patient information leaflets	https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/41/ALL/		

A note about: Adderall and Adderall XR (Shire US).

These are formulations licensed in the US and not available in the UK. They are an immediate release (Adderall) and a sustained release (Adderall XR) preparation containing mixed salts of amfetamine and dexamfetamine.

Patients prescribed Adderall or Adderall XR who move to Oxfordshire as temporary residents will be asked to obtain a supply from the country they were prescribed this.

A switch from Adderall (IR or XR) to dexamfetamine at a 1:1 dose equivalence may be necessary.

Dexamfetamine needs to be taken in divided doses, so if the patient was taking Adderall XR, consideration may need to be given to using lisdexamfetamine or other treatment options. Any patients treated for ADHD in Oxfordshire need to meet ICD-10 diagnostic criteria.

Table 3. Potential interactions with stimulant medications – refer to SPCs for complete information

		Nature of interaction	
Drug/class	**Management**	**Methylphenidate**	**Lisdexamfetamine and dexamfetamine**
Alcohol	The manufacturer suggests avoiding alcohol.	May increase methylphenidate levels and exacerbate CNS effects	May exacerbate CNS effects of amfetamines
Alpha agonists	Monitor blood pressure	E.g. clonidine: usually uneventful, but adverse effects on blood pressure and pulse may occur. The manufacturer of dexamfetamine also states that clonidine may also increase duration of the action of dexamfetamine.	
Anticoagulants	Monitor INR if drug is started or stopped	Evidence indicates that an interaction is unlikely, never-the-less, manufacturers recommend caution and monitoring.	
Anticonvulsants	Monitor for increased anticonvulsant adverse effects, take plasma levels or reduce the dose if appropriate. Consider dose adjustments if stimulant is started or stopped.	Manufacturers state that concentrations of some anticonvulsants may be increased (e.g. phenytoin, phenobarbitone, primidone). This is not an established interaction and clinical significance unclear.	Manufacturer states that absorption of some anticonvulsants may be delayed, and metabolism may be inhibited, however the clinical significance is unclear.
Antidepressants	SSRIs & TCAs: Concurrent use of SSRIs is often beneficial but monitor for increased side effects, including serotonin syndrome. Concomitant use with TCAs may increase the risk of cardiovascular adverse effects.	Evidence for an interaction with SSRIs is limited to case reports only. Methylphenidate may increase plasma levels of some TCAs.	Plasma concentrations of some SSRIs and TCAs may be increased by amfetamines, and possibly vice versa.
Antihypertensive medication	Monitor blood pressure	May decrease the effectiveness of antihypertensives including some diuretics	
Antipsychotics	Avoid combined use or use with caution	Dopamine antagonists oppose central dopamine enhancing effects	
Beta blockers	Caution when co-prescribing	NA	May result in severe hypertension
Opioid analgesics	Monitor for increased opioid effects and adjust dose as appropriate	NA	Amfetamines potentiate the analgesic effect of opioid analgesics
Serotonergic medication	Monitor for symptoms of serotonin syndrome and discontinue medication if necessary.	Increased risk of serotonin syndrome: mental-status changes (agitation, hallucinations, coma), autonomic instability (tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (nausea, vomiting, diarrhoea)	

Atomoxetine

A brief summary of information is included below, but for full prescribing information please refer to the manufacturer's SPCs at: www.medicines.org.uk/emc/

Licensed indications	Licensed as part of a comprehensive treatment programme for ADHD in children (6 years and over), adolescents and adults.
Formulations included in shared care	• Capsules: 10mg, 18mg, 25mg, 40mg, 60mg, 80mg, 100mg • Liquid: 4mg/ml oral solution – restricted for use in patients who can't swallow tablets.
Contraindications and precautions	Refer to the manufacturer's SPC at www.medicines.org.uk/emc/
Dose, titration and administration	Administer once daily in the morning with or without food. The dose may be given as two evenly divided doses in the morning and late afternoon/early evening if unwanted effects are problematic.

Patient weight	Starting dose	Recommended maintenance dose
<70 kg	0.5 mg/kg/day	1.2 mg/kg/day
>70 kg	40 mg/day	80 mg/day

The maximum recommended total daily dose is 120 mg. The safety of single doses >120 mg and total daily doses >150 mg have not been systematically evaluated.

Onset of action	Atomoxetine does not produce a quick change in symptoms. Onset of action is gradual and is generally seen within three to six weeks but can sometimes take longer.
Missed doses	If one dose is missed, resume the next day. Re-titration shouldn't be necessary. If patients have missed several days or weeks of medication, re-titration may be appropriate and should be based on the patient's previous tolerability and response
Discontinuation	Atomoxetine is not associated with withdrawal symptoms if it is stopped suddenly. It can therefore be discontinued without the need for tapering of the dose if necessary, however as symptoms of ADHD may return, it may be more appropriate to taper the dose when stopping treatment if possible.

Adverse effects – some of the more common effects. See SPC for full list

Frequency	Effect	Additional information and management
Very common (≥ 1/10)	Headache	Usually transient. Paracetamol may help.
	Insomnia	Dose timing or formulation change may be necessary.
Common (≥ 1/100 to < 1/10)	Reduced appetite and weight loss	See monitoring schedule for guidance.
	Nausea, vomiting, GI upset	Mainly at the start of treatment and usually transient. Might be helped by taking dose with food.
	Tachycardia	See monitoring schedule for guidance.
	Dizziness	Usually transient.

	Changes in mood	Development of new or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.
	Dysmenorrhea	A change in medication may be necessary
	Erectile and ejaculatory dysfunction	A change in medication may be necessary.
Rare (≥ 1/10,000 to < 1/1,000)	Jaundice and hepatic damage	If there are signs and symptoms of liver dysfunction or of haematological abnormalities, discontinue the medication and perform appropriate blood tests. There is no evidence for regular blood testing during treatment where no symptoms are present.

Interactions

Medication	**Effect**	**Management**
CYP2D6 inhibitors, e.g. fluoxetine, paroxetine.	May markedly increase atomoxetine levels	Dose adjustment and slower titration of atomoxetine may be necessary in those patients who are also taking CYP2D6 inhibitor drugs. Monitor for any increase in atomoxetine adverse effects.
Drugs that affect noradrenaline, e.g. venlafaxine, imipramine, mirtazapine, pseudoephedrine, phenylephrine.	Potential for additive or synergistic pharmacological effects.	Monitor for adverse effects.
Drugs which can increase blood pressure.	Possible additive effects on blood pressure.	Monitor blood pressure when drug is started.
Antihypertensive drugs	Atomoxetine may potentially increase blood pressure and therefore decrease the effectiveness of antihypertensive medication.	Monitor blood pressure.
Salbutamol (or other $beta_2$ agonists) – high dose nebulised or oral or intravenous administration.	May cause increase in heart rate and blood pressure due to additive side effects.	Monitor BP and pulse.
QT interval prolonging drugs (such as neuroleptics, class IA and III anti-arrhythmics, moxifloxacin erythromycin, methadone, mefloquine, tricyclic antidepressants, lithium or cisapride).	Potential for an increased risk of QT interval prolongation when administered with other QT prolonging drugs.	No extra monitoring indicated unless ongoing QTc problem.
Drugs that lower seizure threshold, e.g. antidepressants, neuroleptics, mefloquine, bupropion, tramadol.	Seizures are a potential risk with atomoxetine.	Consider using alternative treatments that do not lower the seizure threshold where possible, otherwise use with caution at the lowest effective doses.

Patient information leaflets	https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/11/ALL/

Guanfacine

A brief summary of information is included below, but for full prescribing information please refer to the manufacturer's SPCs at: www.medicines.org.uk/emc/

Licensed indications	Licensed as part of a comprehensive treatment programme for ADHD in children (6 years and over), and adolescents where stimulants are not suitable, not tolerated or have been ineffective. Indicated within NICE guidelines, for patients 5 - 17 years old where they cannot tolerate methylphenidate **or** lisdexamfetamine or their symptoms have not responded to separate 6-week trials of lisdexamfetamine **and** methylphenidate, having considered alternative preparations and adequate doses. Guanfacine is not licensed for use in adults.
Formulations included in shared care	Intuniv prolonged release tablets 1mg, 2mg, 3mg, 4mg
Contraindications and precautions	Refer to the manufacturer's SPC at www.medicines.org.uk/emc/
Dose, titration and administration	Dose is based on age and weight. Starting dose is 1 mg taken orally once a day in the morning or evening. Tablets should not be crushed, chewed or broken before swallowing as this increases the rate of release. The tablet can be taken with or without food, but avoid taking with grapefruit juice or a high fat meal, as this significantly increases exposure. Maintenance dose range is 0.05 - 0.12 mg/kg/day depending on response and tolerability. Dose adjustments may occur at any weekly intervals after the initial dose in increments of not more than 1 mg per week.

Dose Titration Schedule for ages 6-12 years				
Weight Group	Week 1	Week 2	Week 3	Week 4
25 kg and up Max Dose= 4 mg	1 mg	2 mg	3 mg	4 mg

Dose titration schedule for ages 13-17 Years*							
Weight Group[a]	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7
34-41.4 kg	1 mg	2 mg	3 mg	4 mg			

Max Dose= 4 mg							
41.5-49.4 kg Max Dose= 5 mg	1 mg	2 mg	3 mg	4 mg	5 mg		
49.5-58.4 kg Max Dose= 6 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	
58.5 kg and above Max Dose= 7 mg	1 mg	2 mg	3 mg	4 mg	5 mg	6 mg	7 mg

** Adolescent subjects must weigh at least 34 kg.*

Onset of action	Guanfacine does not produce a quick change in symptoms. Onset of action is gradual and is generally seen within two to four weeks at a full dose.		
Missed doses	If one dose is missed, resume the next day. If two or more consecutive doses are missed, re-titration is recommended based on the patient's tolerability to guanfacine.		
Discontinuation	Guanfacine should not be discontinued abruptly due to the risk of rebound hypertension. When stopping, the dose must be tapered by 1 mg every 3 - 7 days. Blood pressure and pulse should be monitored. Consider trial periods off medication, preferably during school holidays.		
Adverse effects – some of the more common effects	**Frequency**	**Effect**	**Additional information and management**
	Very common (≥ 1/10)	Headache	Usually transient. Paracetamol may help.
		Somnolence	This effect should be monitored during titration and then every 3 months for the first year. It may occur in up to 40% of patients but is usually transient, taking a few weeks to wear off. It might be helped by taking the dose at night, slowing the titration or reducing the dose.
		Abdominal pain	May be helped by taking with food (but not a high fat meal).
	Common (≥ 1/100 to < 1/10)	Nausea, vomiting, diarrhoea, constipation	Mainly at the start of treatment and usually transient. Might be helped by taking dose with food (but not a high fat meal).
		Bradycardia	May be seen during the first few weeks of treatment and is usually transient. See monitoring schedule for guidance.
		Hypotension	May be seen during the first few weeks of treatment and is usually transient. See monitoring schedule for guidance.
		Orthostatic hypotension	
		Dizziness	
		Changes in mood	Development of new or worsening of pre-existing psychiatric symptoms should be monitored at every dose change and at least 6-monthly.

	Weight gain	Increases in BMI may occur. See monitoring schedule for guidance.	

Interactions

Medication	Effect	Management
Lisdexamfetamine	The combination modestly increases guanfacine plasma concentrations	Not expected to be clinically meaningful
CYP3A4/5 inhibitors (e.g. clarithromycin)	Guanfacine levels can be significantly elevated by moderate or strong inhibitors	A 50% reduction of the guanfacine dose is recommended
CYP3A4/5 inducers (e.g. rifampin, carbamazepine, phenytoin, St. John's Wort)	Guanfacine levels may be reduced	Re-titration of the guanfacine up to the maximum recommended dose may be necessary
OCT1 substrates (e.g. Metformin)	Guanfacine may be an inhibitor of OCT1. Combination may increase plasma levels of OCT1 substrates	Monitor for adverse effects and consider dose decrease of OCT1 substrate
QT prolonging medication	Guanfacine can cause bradycardia which pre-disposes to conduction disorders	Monitor heart rate
CNS depressants (e.g. alcohol, sedatives, hypnotics, benzodiazepines, barbiturates, and antipsychotics)	Potential for additive pharmacodynamic effects such as sedation, hypotension or QT prolongation	Use with caution
Valproic acid	Combination can cause increased valproic acid levels. The mechanism is unknown	Monitor patients for additive CNS effects. Consider monitoring serum valproate levels and reducing dose if indicated
Antihypertensives	Potential for additive pharmacodynamic effects such as hypotension and syncope	Monitor blood pressure
Grapefruit juice	Moderately inhibits metabolism and may increase guanfacine levels	Avoid.

Patient information leaflets

https://www.choiceandmedication.org/oxfordhealth/printable-leaflets/patient-information-leaflets/11/ALL/

6. CONTACT DETAILS

Warneford Hospital switchboard	01865 901000
CAMHS Neurodevelopment Pathway	01865 902447
Oxford Health Medicines Advice Service	Tel: 01865 904365 medicines.advice@oxfordhealth.nhs.uk
OUH Consultants / paediatrics	Flaudia Petrone Community Paediatric Consultant. 01865 231 997

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